REMARKS

I. Status of the claims

Claims 1, 3-6, and 9-25 are pending. Claims 2, 7, and 8 were canceled previously, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to canceled subject matter. Claims 6 and 10-24 are withdrawn.

Purely for the sake of expediting examination, Applicants amend claims 1, 5, and 25 to recite a "CYP3A4 family gene" instead of a "P450 3A family gene." For the same reason, Applicants amend claim 9 to clarify that the recited cell or tissue is obtained from a "liver or small intestine" organ of the claimed mouse. Support for "liver"- and "small intestine"-specific expression is found in Example 4 (page 77, lines 17-20).

II. Contrary to the Office's understanding, the E22 chromosomal fragment is *not* essential to the claimed method; moreover, the claimed mouse contains a human chromosome fragment that *is* produced by a repeatable and predictable method disclosed in the specification

Claims 1-5, 8, 9, and 25 are rejected under 35 U.S.C. § 112, first paragraph. Office Action at page 2. The Office contends that the specification teaches the "generation of the E22 fragment" by microcell-mediated chromosomal transfer (MMCT) and that, therefore, E22 is "essential" to the claimed method. Hence, according to the Office, only a mouse containing E22 is enabled. See the Office Action at page 4, lines 3-4, and page 5, lines 11-17.

The sole basis for the rejection lies in the allegation that the specification fails to disclose a method for "predictably" producing a human chromosome fragment containing the recited cytochrome gene(s): "the claimed invention is not found to be enabled, because the fragment, which is used in the working examples is not found to be predictably produced." Office Action at page 6, lines 14-15.

The Office invites Applicants to "point to specific support in the specification by page and line number" if they "feel that the production of [the] E22 fragment is disclosed by a repeatable process" (page 4, lines 11-13). Otherwise, the Office insists that Applicants deposit the E22 fragment under the terms of the Budapest Treaty, whereafter "the claims will be limited to the E22 fragment" (page 4 and page 5, lines 9-10).

(a) The specification teaches a non-spontaneous method for producing *any* chromosome fragment that contains a CYP3A4 gene

At issue is not whether E22 *per se* can be repeatedly produced, but rather whether the specification teaches a non-spontaneous method for producing *any* chromosome fragment that contains a CYP3A4 gene.

Accordingly, Applicants not only point to explicit written description for a repeatable fragmentation method but they also reiterate that E22 is not the only fragment disclosed in the specification. It is unnecessary and, indeed, it is inappropriate to limit Applicants' invention to a biological deposit for E22. This is so because E22 is representative only of a particular fragment, among the very many fragments that can be made by the present invention.

In this vein, Applicants would emphasize an underlying purpose of the claimed invention, which is to produce a mouse containing a human chromosome fragment that expresses a CYP3A4 cytochrome gene. This CYP3A4-expressing mouse is useful for *in vivo* evaluation of drug metabolism because it is well known that cytochrome genes mediate the way in which the body processes pharmaceuticals. The claimed mouse is a convenient vehicle, therefore, for studying physiological, biochemical, and metabolic effects of various drugs that are fed or administered to it.

With this underlying purpose in mind, Applicants refer to the specification, which discloses two basic fragmentation methods:

(1) irradiation-based spontaneous fragmentation, and

(2) site-specific fragmentation.

The basis for rejecting the claims focuses only on that portion of the specification that deals with (1), the irradiative fragmentation method. As Applicants reiterate in this paper, other portions of the specification clearly disclose the second method, namely the precise truncation of a human chromosome to obtain a fragment delineated by specifically desired termini.

(b) The fragment shown in Ohshima Declaration (the "Ohshima fragment") is produced by the specific cleavage method disclosed in the specification

To elaborate, methods for obtaining the claimed mouse are disclosed in detail from page 26, line 26 to page 43, line 14 of the present specification. Based on this disclosure, the skilled person can obtain the inventive mouse by (i) making human chromosome fragments, (ii) introducing those fragments into mouse cells, (iii) selecting a cell comprising a fragment comprising a CYP3A4 gene, and then (iv) breeding a chimeric mouse using that selected cell.

While the specific E22 fragment is obtained by irradiation-mediated fragmentation, the fragment shown in Ohshima Declaration (the "Ohshima fragment") is produced by the specific cleavage method disclosed in the specification.

Applicants emphasize that one reason they submitted the Ohshima Declaration was in response to the Examiner's request for evidence demonstrating the repeatability of *any* disclosed fragmentation method. Hence, Dr. Ohshima followed the non-irradiation fragmentation method steps of the specification's Examples to produce a human chromosome fragment containing a cytochrome gene cluster.

Contrary to the Examiner's impression, Dr. Ohshima did not set out to reproduce the *exact* chromosome fragment disclosed in Example 23, E22. Rather, the declarant proved, as the Examiner explicitly requested, that the disclosed fragmentation methodology is repeatable.

The Ohshima fragment actually is obtained by a methodology that differs from that used to obtain E22 (see below). The Ohshima fragment is not the same as E22. The Ohshima fragment is delineated by loci AF006752 and AC004922, which is shorter than E22 fragment, and was not produced randomly or spontaneously.

(c) Details concerning creation of the Ohshima fragment and the fragment of the specification

The Ohshima fragment was produced by truncating human chromosome 7 specifically at a telomere site introduced at the AF006752 locus, in accordance with the present examples, *e.g.*, Examples, 1, 14, 19, and 23. See also Exhibit A, Figure 3 of the Ohshima Declaration.

The Ohshima fragment was created from the DF141 clone disclosed in Example 19. See page 124, line 15 and page 126, lines 16-24. DF141 was obtained by deliberately inserting a telomere sequence at the AF006752 site of the human chromosome 7 of Example 14 and then precisely cleaving it at that specific junction. The fragment that has come to be known here as the "Ohshima fragment" was created subsequently by introducing a loxP site into the AC004922 site of DF141 and then cleaving it at that loxP site with Cre recombinase.

To recap, Dr. Ohshima introduced the same H5 clone harboring full-length human chromosome into DT-40 cells, as described in Example 14. He then site-specifically cleaved that clone at its AF006752 locus by following the telomere truncation method steps disclosed in Example 19 to generate the DF141 clone.

In Dr. Ohshima's case, he then cleaved the DF141 clone specifically at its AC004922 locus as shown in Figure 3 of Exhibit A. The specification, however, cleaves the DF141 clone at its COLIA2 locus. See Example 23, which uses a "COL1A2-CYP3A-AF006752tel."

Nevertheless, both in Dr. Ohshima's experiment and in the experiment of Example 23, the cleaved DF141 clone – be it cleaved at AC004922 or COLIA2 – was subsequently translocated onto the chromosome 14 fragment, SC20. In *both* cases, therefore, the Ohshima fragment and the Example 23 fragment each comprise portions of human chromosomes 7 and 14.

(d) Ohshima's mouse and the mouse disclosed in the Examples both meet the recited requirements of the mouse of claim 1

Applicants point out that claim 1 requires only the presence of *any* human chromosome fragment that is not integrated into the mouse cell genome, wherein the human chromosome fragment expresses at least one human cytochrome CYP3A4 family.

The mouse produced by Dr. Ohshima certainly meets this requirement and is consistent with the underlying premise of the claimed invention, which is to produce a mouse with a human chromosome fragment that contains the CYP3A4 gene family. See paragraphs 11 and 12 at page 2 of the Ohshima Declaration, where Dr. Ohshima attests that the resultant fragment was proven by PCR to "contain the same CYP3A cluster, including the CYP3A4, CYP3A5, and CYP3A7 genes" as the chromosome fragment disclosed in the specification.

The specification therefore explicitly teaches that such a CYP3A4-expressing chromosome fragment can be created by telomere truncation followed by site-specific chromosome fragmentation, as is the case for the disclosed COL1A2-CYP3A-AF006752tel fragment and the Ohshima fragment; and not necessarily by irradiation-mediated fragmentation.

(e) The rifampicin-induced phenotype observed in the created mice is attributed to a chromosome 7 fragment that contains a CYP2A4 gene, not to two different chromosomal fragments

The Examiner questions whether the phenotype of the mouse produced by the inventive method is the same as the claimed mouse because "the specification indicates that the mice in Examples 24-26 also have an additional fragment from chromosome #14, SC20." Office Action at page 7.

Applicants clarify that the Examples referenced by the Examiner actually teach the *translocation* of the specific chromosome 7 fragment onto a chromosome 14 fragment. Hence, as Applicants related above, both the Ohshima fragment and the Example 23 fragment were each "subsequently translocated onto the chromosome 14 fragment, SC20."

Applicants point to the subsection of Example 23 entitled "Site-specific translocation of human chromosome 7 fragment to chromosome 14 fragment, SC20 ..." at page 136, lines 20-22, and to the disclosure at page 139, lines 11-27, to support this clarification.

The latter disclosure relates that the inventors employed chromosome 7- and chromosome 14-specific probes to "confirm that signals derived from both probes were observed on the same chromosome" (emphasis added; page 139, lines 21-22). This resultant clone, "chromosome #7-HAC," was subsequently used in Examples 24-26 referenced by the Examiner.

The Examiner erroneously interprets the observed rifampicin-induced phenotype as a direct consequence of two distinct chromosome fragments. In actuality, the phenotype results solely from rifampicin-induced expression of a CYP3A4 family gene present in the human chromosome 7 fragment.

Example 4 of the present specification, as corroborated in the Ohshima Declaration, thus teaches that cells of the liver and small intestine of the claimed mouse can be induced by rifampicin to express CYP3A4. See page 77, lines 16-20.

This does not mean that other chromosomes are excluded from a cell of the claimed mouse. The transition of claim 1 ("comprises") permits the presence of artificial chromosomes other than the CYP3A4-containing fragment. Indeed, other chromosomes certainly do exist in the cell of the claimed mouse – its own endogenous chromosomes, for instance.

(f) The specification, as corroborated by the Ohshima Declaration, teaches how to produce a CYP3A4-containing human chromosome fragment repeatably, without using irradiation, and how to make a mouse containing that fragment

The specification fully supports and enables the mouse of claim 1, which comprises a CYP3A4-containing fragment that has been produced by a repeatable method, and which exhibits a phenotype that is directly attributed to expression of genes on that fragment, especially in the mouse's liver and small intestine.

For these reasons, the specification more than sufficiently enables the skilled person therefore under the requirements of 35 U.S.C. § 112, first paragraph, to repeatedly and successfully produce a human chromosome fragment other than E22 that contains CYP3A4 genes, and to produce a mouse containing that fragment.

Applicants therefore assert that the claimed invention is enabled and ask that the Office withdraw this rejection.

III. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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